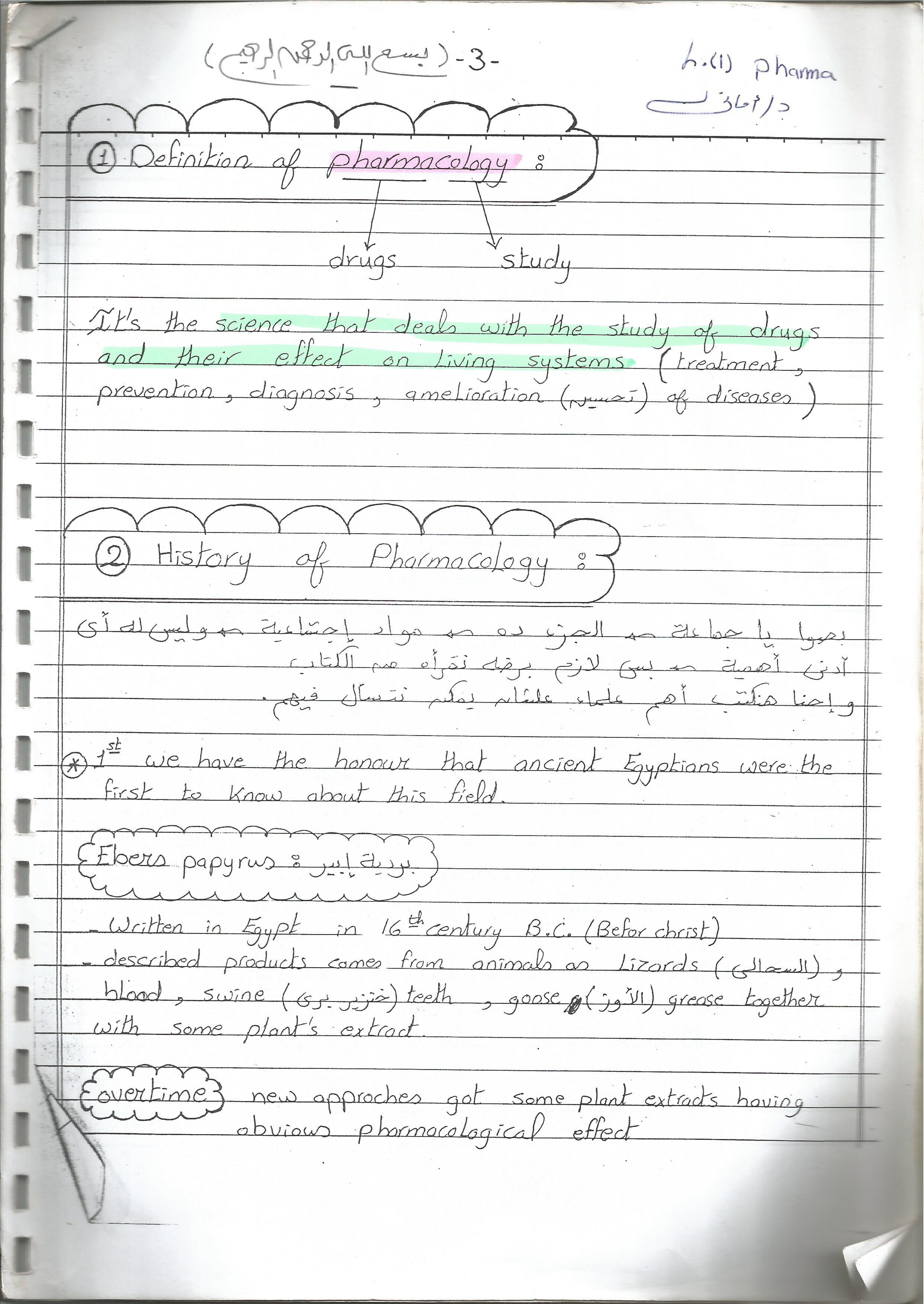


① Definition of pharmacology :

pharmaco → drugs
logy → study

It's the science that deals with the study of drugs and their effect on living systems (treatment, prevention, diagnosis, amelioration (تحسين) of diseases)

② History of Pharmacology :

بصوا يا جماعة ـــ الجزء ده ـــ مواد إجتماعية ـــ وليس له أى
أدنى أهمية ـــ بس لازم برضه نقرأه من الكتاب
وإحنا هنكتب أهم علماء علشان يمكن نتسأل فيهم.

(*) 1st we have the honour that ancient Egyptions were the first to know about this field.

Ebers papyrus : بردية إيبر

- Written in Egypt in 16th century B.C. (Befor christ)
- described products comes from animals as Lizards (السحالى), blood, swine (خنزير برى) teeth, goose (الأوز) grease together with some plant's extract.

overtime new approches got some plant extracts having obvious pharmacological effect

eg :

① Poppy → opium → morphine → analgesic
② Cinchona → extract → antimalarial drug.

Materia media

⊛ a Science developed to understand origin, preparation, therapeutic applicatn, of medicinal comp.

⊛ it said that every disease has a cause for which there's a specific drug (remedy)

⊛ The drug administratn, is based on testing dose - response relationship

In 1897

Felix Hoffman developed aspirin (analgesic).

In 1971

Sir John Vane discovered mode of action (MOA) of aspirin

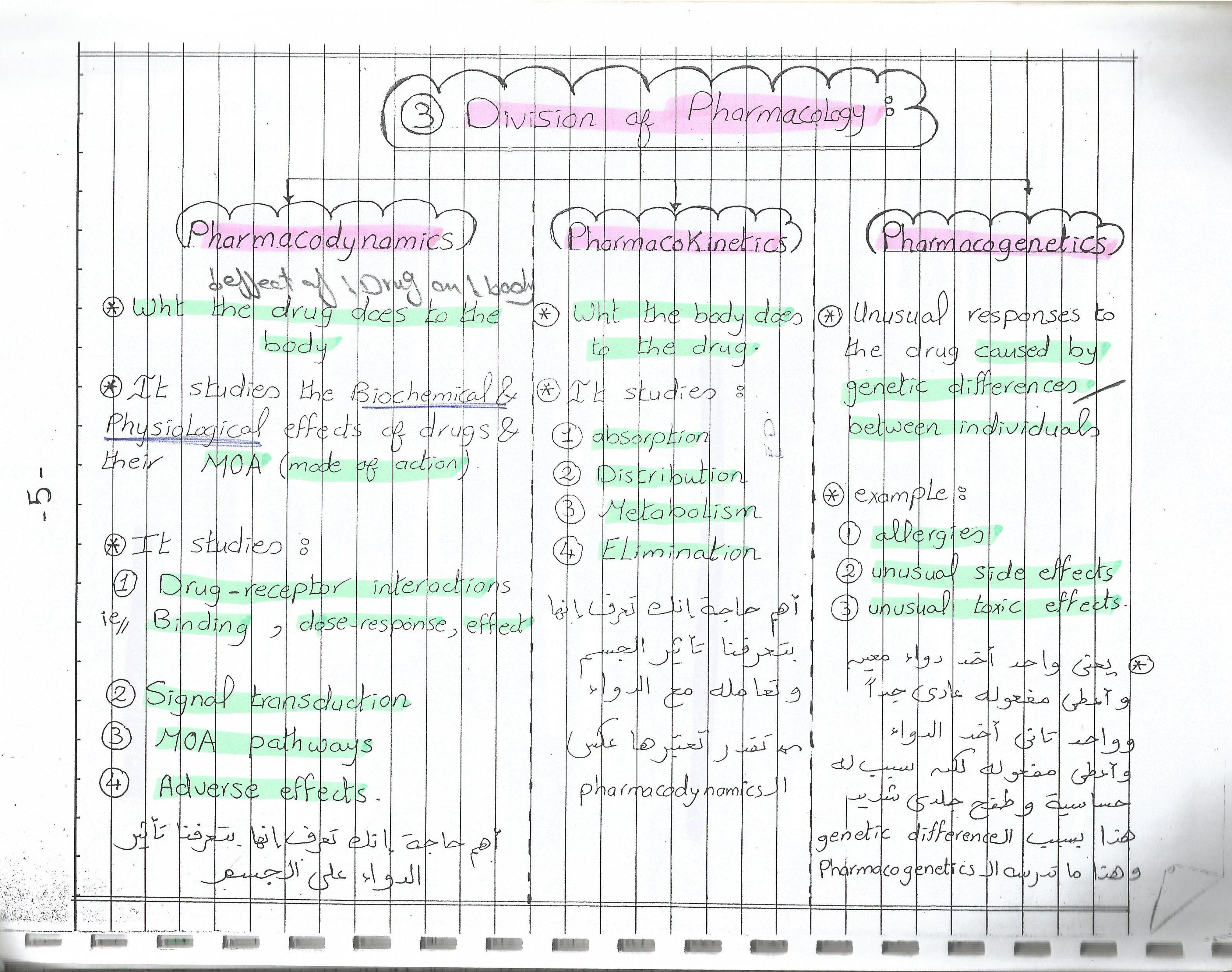
In 1908

Paw Ehrlich described drug - receptor binding by a very famous & important sentence saying

"Agents do not act unless they are bound"

وكده نبقى خلصنا المواد الإجتماعية ونبتدي نخش ف المهم.

ركزوا أرجوكم



③ Division of Pharmacology :

Pharmacodynamics

b(effect of (Drug on (body)

* Wht the drug does to the body
* It studies the Biochemical & Physiological effects of drugs & their MOA (mode of action)
* It studies :
  1. Drug-receptor interactions ie// Binding , dose-response, effect
  2. Signal transduction
  3. MOA pathways
  4. Adverse effects.

أهم حاجة إنك تعرف إنها بتعرفنا تأثير الدواء على الجسم

PharmacoKinetics

* Wht the body does to the drug.
* It studies :
  1. absorption
  2. Distribution
  3. Metabolism
  4. Elimination

أهم حاجة إنك تعرف إنها بتعرفنا تأثير الجسم وتعامله مع الدواء
ممكن تقدر تعتبرها عكس الـpharmacodynamics

Pharmacogenetics

* Unusual responses to the drug caused by genetic differences between individuals
* example :
  1. allergies
  2. unusual side effects
  3. unusual toxic effects.

* يعني واحد أخد دواء معين وأعطى مفعوله عادي جداً
وواحد تاني أخد الدواء وأعطى مفعوله لكنه سبب له حساسية وطفح جلدي شديد
هذا بسبب الـgenetic difference
وهذا ما تدرسه الـPharmacogenetics

(4) Definition of drug :

(*) They are chemical substances (agents) that uniquely interact with specific target molecules (receptors) in the body → thereby producing a Biological effect

(*) They can be stimulatory or// inhibitory.

(*) They affect Living processes

(*) They are used in treatment, prevention, diagnosis or// amelioration (تحسين) of diseases

(5) Drugs Produce their effects virtue (عن طريق)

1. Acidic or// Basic properties eg : antacids
2. Surfactant properties eg : Amphotericin B
3. Ability to denature proteins eg : Astringent
4. Osmotic properties eg : Laxatives & diuretics.
5. Physicochemical interactions with membrane Lipids
   eg : general & local anaethetics.

دلوقتي هنتكلم عن topic جديد وحلو ولازم يتفهم بكل ما فيه

Receptors

(*) Most drugs combine é specific receptors to produce a particular response.

(*) This association or binding take place by precise physiological & sterile interactn between specific groups of the drug & the receptor.

Protein in a body may be in form of

أصلاً يا جماعة ده أي Protein عبارة عن

Carrier (or) Receptor (or) enzyme

Receptor → has 2 main types

Membrane bound receptors

يعني receptor موجودة من الخارج على سطح ال cell على ال membrane

has 3 types :

1. (G protein linked) receptors as muscarinic, noradrenergic, dopaminergic
2. (Enzyme linked) as Tyrosine Kinase
3. (Ligand gated channels) as Nicotinic, GABA, Glutamate

Intracellular & nuclear receptors

يعني recept. موجودة داخل ال cell أو في ال nucleus

examples :

1. hormone receptors.
2. Autacoid eg → histamine
3. Growth factors
4. Insuline

- Drug interact and bind c̄ ↓ Receptor by specific gp.
- after ↓ binding ↓ signals Appear Then Amplified and produce ↓ effect

Drug-receptors interactn :

هنشرح بالعربي الأول وبعدين نقول الكلميتين اللغة.

الدواء بيمسك في الـ receptor ← هنا يؤدي إلى ظهور signal ← الـ signal ده بتحول بعض الـ events أو cellular activities ← التي تهدف إلى تضخيم الـ signal.
← لما الـ signal تتضخم الـ response اللي إحنا عايزينه مع (effect) الـ drug بيظهر

⊛ It serves as a signal to trigger cascade (فيضان) of events (collection of cellular responses)

⊛ These events serve to amplify the signal & Produce effect.

طيب إيه هي الـ events دي يا عم إنت؟

⊛ لما الدواء بيمسك في الـ receptor ← هناك بعض المواد بتطلع تدعى effectors ← وهذه الـ effectors بتتسبب في ظهور بعض المواد الأخرى تدعى 2nd messenger التي تسبب تغيرات في الـ cell activity و ظهور الـ cell response للدواء المعطى

Effectors : "they are molecules which translate the drug-receptor interactions into changes in cellular activity"

- Drug + Receptor —Binding→ effectors → 2nd messenger → Changes in ↓ Cell Activity → Cell Response

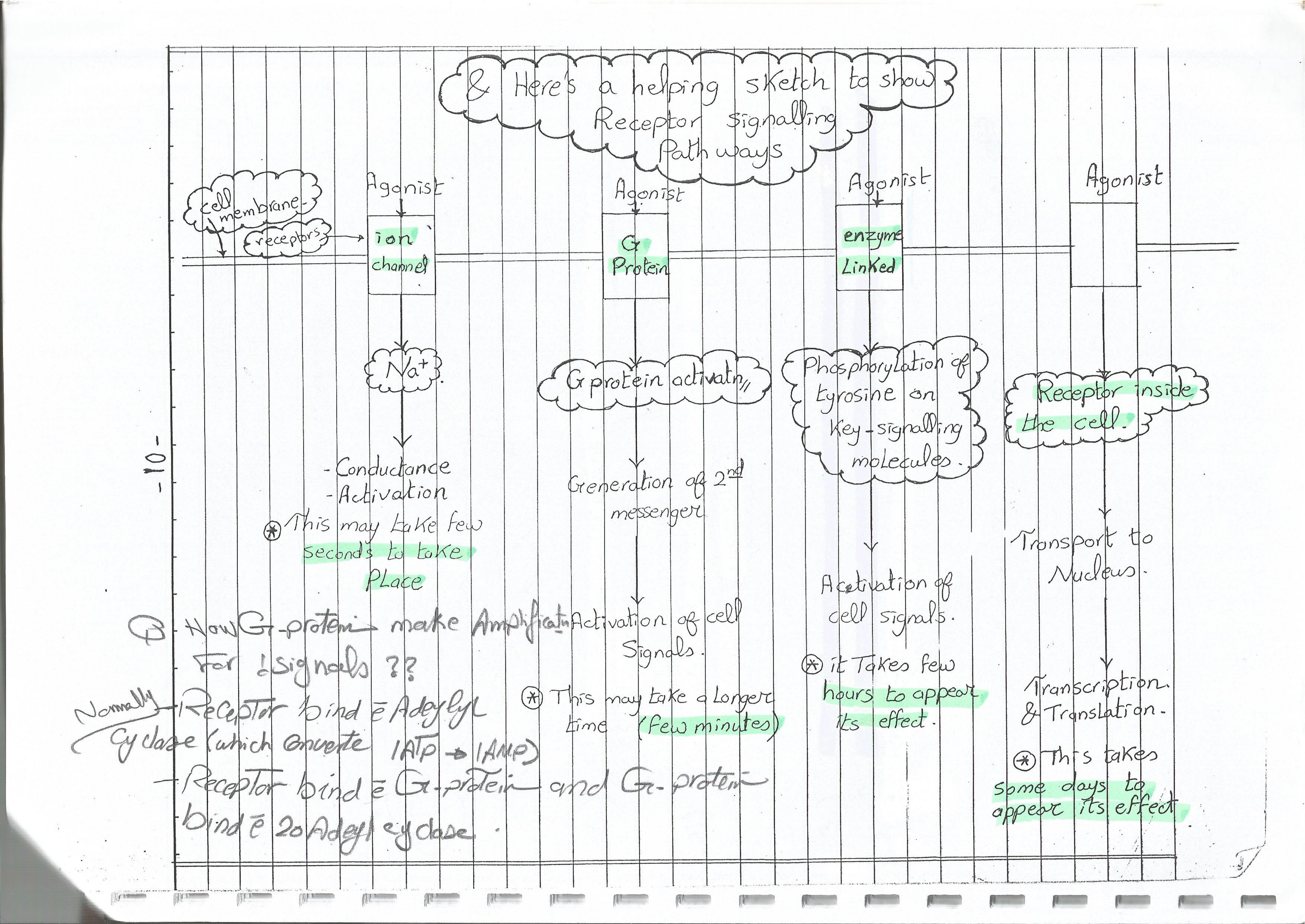
N.B effector → Converts (binding of Drug ē Receptor) to stimulus

Drug + Receptor —Binding Interactn→ Drug-receptor complex
↓ activation
Drug-receptor + effector —transduction→ 2nd messenger
↓
Cascade of changes of cellular activity —Amplificatn of stimulus (signal)→ Response

& Here are Some effectors & their corresponding 2nd messengers

Effector	2nd messenger
Adenylate cyclase (AC)	CAMP } أخذناهم في الـ Biochemistry الـ term السابق
Guadenylyl cyclase (GC)	CGMP
Phospholipase A_2 (PLA_2)	Arachidonic acid
Phospholipase C (PLC)	DAG → diacyl glycerol IP_3 → inositol triphosphate
Nitric oxide synthase	Nitric oxide (No)
Ions channels	Na^+, K^+, Ca^{+2}

الدكتورة لم تهتم بالـ examples أوي بس لكم هناخدها تاني بعد كده بس على العموم إحنا هنذاكرها طبعاً


& Here's a helping sketch to show Receptor signalling Path ways
Cell membrane
receptors
Agonist
ion channel
Na+
- Conductance
- Activation
* This may take few seconds to take Place
Agonist
G Protein
G protein activatn
Generation of 2nd messenger
Activation of cell Signals.
* This may take a Longer time (Few minutes)
Agonist
enzyme Linked
Phosphorylation of tyrosine on Key-signalling molecules.
Activation of cell signals.
* it Takes few hours to appear its effect.
Agonist
Receptor inside the cell.
Transport to Nucleus.
Transcription & Translation.
* This takes some days to appear its effect.
Q How G-protein make Amplification For ↓signals ??
Normally - Receptor bind ē Adeylyl Cyclase (which converte 1ATP → 1AMP)
- Receptor bind ē G-protein and G-protein bind ē 20 Adeyl cyclase.
-10-

* طيب إحنا كده عرفنا تأثير كل molecule من الـ Drug على
كل molecule من الـ receptors

* دلوقتي عايزين نعرف تأثير كمية الدواء وده يرضح تبع الـ

Drug - Receptor interactions :
Theory & assumptions

1.) drug - receptor interactions follows mass action Relationship

2.) This means that only one molecule of drug occupies one receptor reversibly

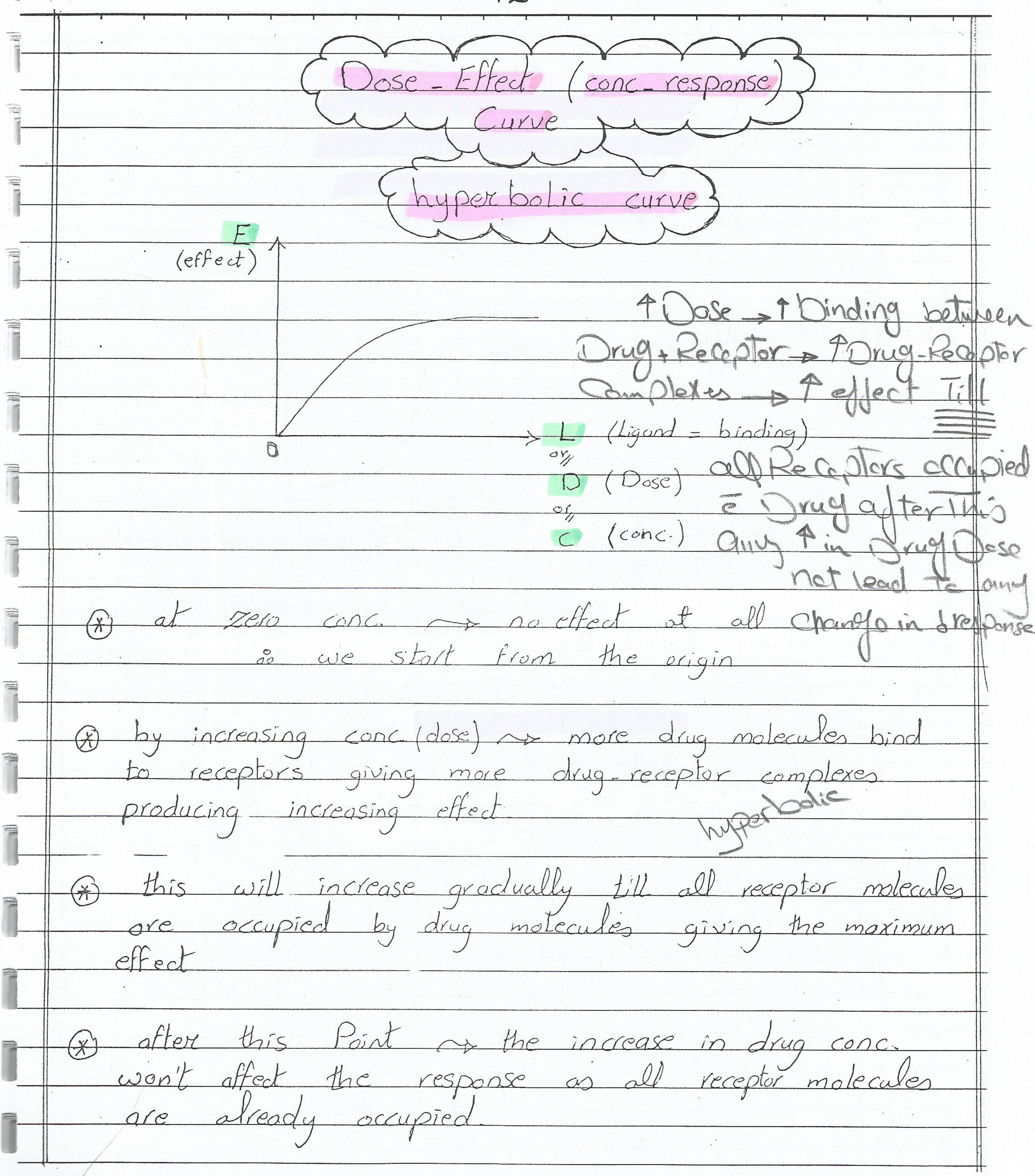
3.) Magnitude of response of cell is proportional to total receptor sites occupied by drug molecules.

why ??? ∴ Response to drug is graded [Dose dependant]

و هنشوف الكلام ده بالـ Curves وتتأكد منه

Dose _ Effect (conc _ response) Curve

hyperbolic curve



↑ Dose → ↑ Binding between Drug + Receptor → ↑ Drug-Receptor Complexes → ↑ effect Till all Receptors occupied c̄ Drug after This any ↑ in Drug Dose not lead to any change in the response

(*) at zero conc. → no effect at all
∴ we start from the origin

(*) by increasing conc. (dose) → more drug molecules bind to receptors giving more drug-receptor complexes producing increasing effect. hyperbolic

(*) this will increase gradually till all receptor molecules are occupied by drug molecules giving the maximum effect

(*) after this Point → the increase in drug conc. won't affect the response as all receptor molecules are already occupied.

By taking Log to Dose to change the hyperbolic Curve to a Sigmoidal Curve

[Sigmoidal Curve]

E (effect)

50%

(ED 50)

Log Dose.

(*) We carried out Log Dose → to get this curve that will help us alot in getting (ED 50)

What's (ED 50)?

It's the Dose that gives 50% of the Effect of the drug.

(*) دلوقتي هننتقل لبعض الـ Expressions الهامة جداً جداً
واللي لازم تكون عارفها وفاهمها وحافظها عن ظهر قلب.
ولازم تعرف الفرق بينهم

(*) Affinity :

It's the ability or tendency of an agonist to bind to its receptor to form a complex.

يعني الـ agonist (drug) اللي عندي ده ← هل له قابلية أو نفس إنه يمسك في الـ receptor ولا لأ

(*) Potency :

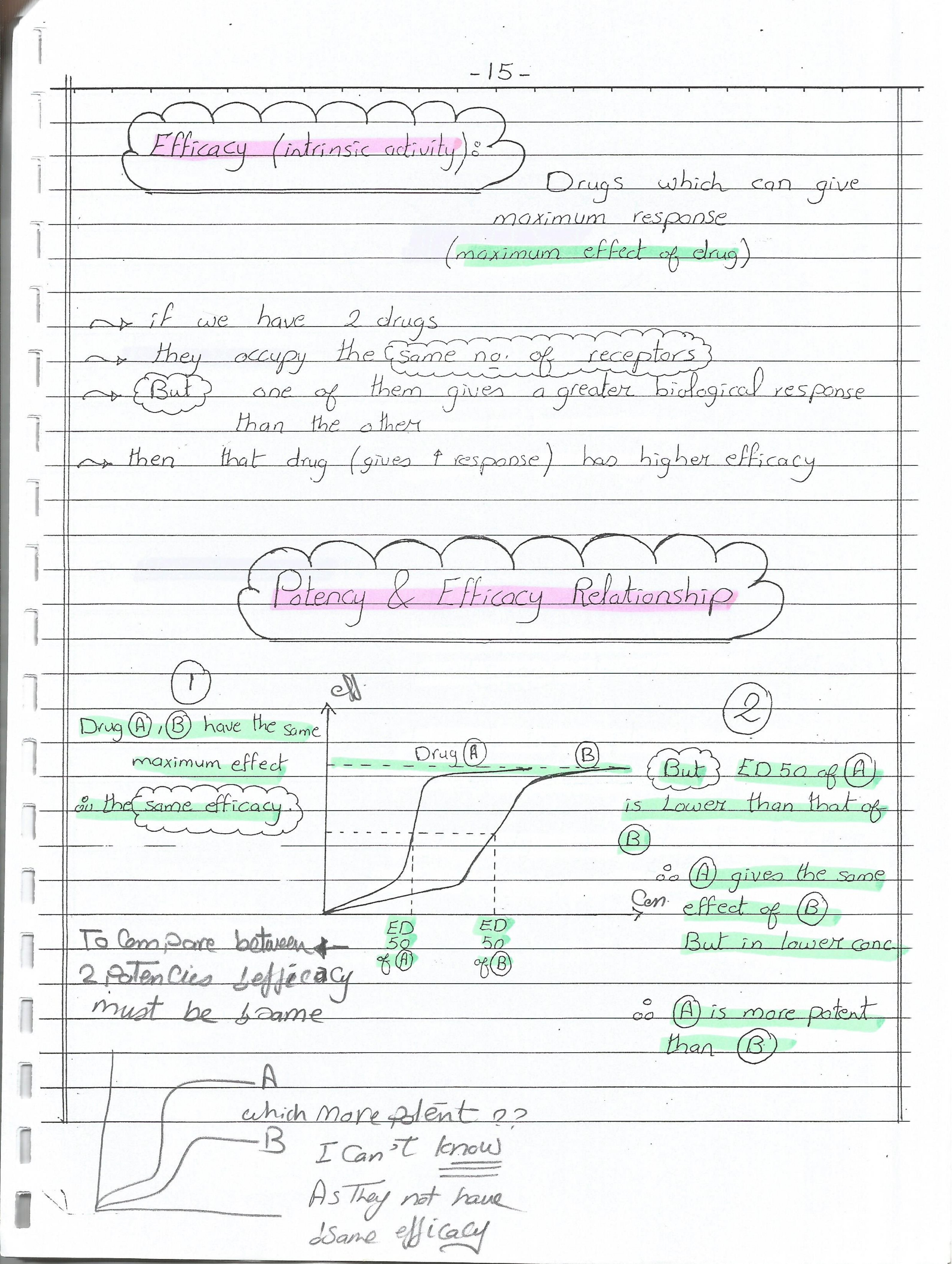
It's a measure of how much drug is required to elicit (produce) a certain response

يعني ← أنا دلوقتي عندي في الصيدلية دوائين المفروض إنهم بيعطوا نفس التأثير لكن واحد منهم لازم آخذ منه 100mg والتاني ممكن آخذ منه 25mg فقط ليعطيني نفس التأثير

← يبقى الدواء التاني (25mg) ← is more potent
و الدواء الأول (100mg) ← is less potent

- what's meaning of Drug A more Potent Drug B ??

This mean That Drug A give Same Action & Response of Drug B but by using Low



Efficacy (intrinsic activity):

Drugs which can give maximum response (maximum effect of drug)

- if we have 2 drugs
- they occupy the same no. of receptors
- But one of them gives a greater biological response than the other
- then that drug (gives ↑ response) has higher efficacy

Potency & Efficacy Relationship

① Drug Ⓐ, Ⓑ have the same maximum effect ∴ the same efficacy.

② But ED 50 of Ⓐ is Lower than that of Ⓑ

∴ Ⓐ gives the same effect of Ⓑ But in lower conc.

∴ Ⓐ is more potent than Ⓑ

To Compare between 2 potencies & efficacy must be same

which more potent ??

I Can't know

As They not have same efficacy

وتعالوا نشوف برضه بعض الـ Expressions المهمة جداً جداً جداً

AGONIST

⊛ Full Agonist :

It's the drug which :

1. has affinity to receptor
2. has intrinsic activity (efficacy)

⊛ Partial agonist :

It's the drug which :

1. has affinity to receptor
2. has (some) intrinsic activity (efficacy)

∴ it binds to receptor but never Produces maximum effect

∴ used only in mild cases but severe cases requires full agonist.

ANTAGONIST

It's the drug (substance) that :
1. has affinity to the receptor
2. has (zero) intrinsic activity (efficacy)

ie// no respons is ever achieved by its binding.

يعني حاجة [illegible] خنيقة كده مرجات ومسكت في الـ receptor ولم تفعل شيئاً.

فـ ممكن نعتبرها إيه؟ ← Blocker للـ receptor.

Types of antagonism :

1) Pharmacological

⊛ Competitive

- binds with the receptor without activating it.
- Prevent binding of agonist.
- as atropine to acetylcholine
- By ↑ dose of agonist we can get rid of antagonist & vice versa.

⊛ Non competitive

- Binds to different site than agonist exerting its antagonistic action via the other binding site

site (B) affects (A) stoping action of agonist.

(2) Chemical

inactivating the agonist chemically
example :
Dimercapol (antagonist) Being used to treat arsenic posoning (agonist)

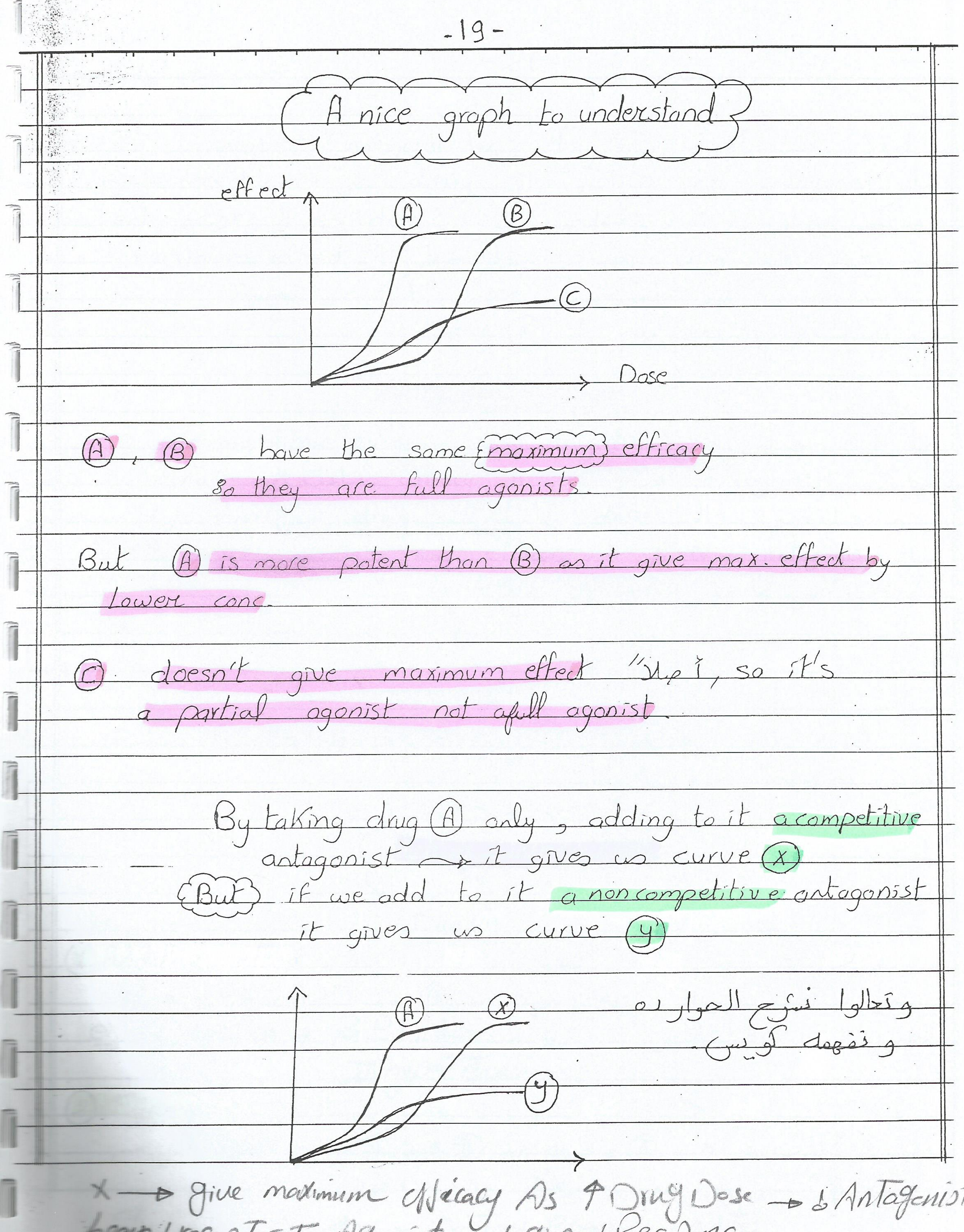
(3) PharmacoKinetic

alters the way by which the body deals with the drug ex phenobarbitone ↑ metabolism of warfarine = so ↓ anti coagulant Activity

(4) PhysioLogic

2 substances act to oppose each other's effect

example : NE (norepinephrine) increases heart beats
while Ach (acetyl choline) decreases heart beats
∴ opposes NE effect
Through Completely different Receptor



A nice graph to understand

(A), (B) have the same {maximum} efficacy so they are full agonists.

But (A) is more potent than (B) as it give max. effect by lower conc.

(C) doesn't give maximum effect "أوي", so it's a partial agonist not a full agonist.

By taking drug (A) only, adding to it a competitive antagonist → it gives us curve (X)
{But} if we add to it a noncompetitive antagonist it gives us curve (Y)

وتعالوا نشرح الحوار ده
وتفهمه كويس

X → give maximum efficacy As ↑ Drug Dose → ↓ Antagonist Leave ↓ receptor to Agonist and give ↓ Response

Y → not ~ ~ ~ As Drugs bind ē all Receptor but its Act is inhibited by ↓ Antagonist

دلوقتي إنت أخدت drug (A) ومعاه competitive antagonist
ـه الـ antagonist ده هينافس الـ drug على الـ receptor شوية
ـه لكن مع زيادة الـ dose بتاعت الـ drug ـه الـ antagonist
سوف يطرد والـ drug سوف يعطي الـ maximum effect
عادي جداً لكن باستخدام Dose أكثر من العادية
وهذا هو ما يعبر عنه الـ curve (X)

ـه طيب ـه لو أخدت drug (A) ومعاه non competitive antagonist
ـه الـ antagonist هيأثر على الـ efficacy بتاعت الـ drug
ومهما تزود الـ dose بتاعت الـ drug مش هيأثر على
الـ antagonist ولا على الـ efficacy
وهذا هو ما يعبر عنه الـ curve (y)

كده إحنا خلصنا الجزء ده وفاضل لنا حتة صغيرة
أوي ـه محاجة في النين.

Drug - interaction

	Drug (A)		Drug (B)		
(1) Additive effect :	1	+	1	=	2

يعني لو أخدت جرعة من (A) وجرعة من (B) ـه الـ effect النهائي هيبقى
مجموع الـ effects بتاعتهم

ex Diuretics + β Blocker → ↓↓↓ hyperTension

(2) Synergism :	1	+	1	>	2

يعني لو أخدت جرعة من (A) وجرعة من (B) هيبقى الـ effect النهائي أكثر من
مجموع الإثنين على بعض ـه يعني بيقووا بعض

ex CCl_3 + C_2H_5OH → DesTroy Liver Completly
Carbon TeTra Chloride — eThanol
- each one have hepatoToxic effect

③ **Potentiation** : (A) 0 + (B) 1 > 1

يعني (A) drug أصلاً ليس له effect لوحده خالص لكن مجرد وجوده بيقوّي الـ effect بتاع (B) ويخلي الـ effect بتاعه أكبر من واحد

ex Barbiturates + Analgesic → ↑ Analgesic effect
also " not analgesic

ومع آخر حاجة

Drug Safety

Therapeutic index (TI)

LD 50 (Median lethal toxic dose) يعني الجرعة اللي لما اديها لـ ١٠٠ انسان ← هيموّت ٥٠ منهم ← مصيبة يعني.

ED 50 (Median effective dose)

* To Calculate the therapeutic index :

$$TI = \frac{LD\,50}{ED\,50}$$

???

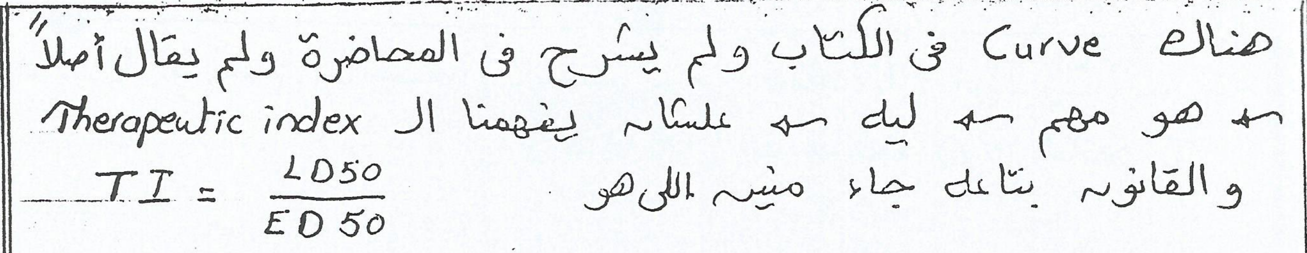
* يعني انهي دواء هيبقى آمن اكتر ؟ اللي عنده TI عالية ولا قليلة ؟!

• طبعاً اللي عنده TI عالية لان دا معناه ان الـ LD50 اللي هي الجرعة اللي بتموّت 50% من الناس هتبقى كبيرة ← Safe ..

i.e. The Safe drugs are those that have a high therapeutic index

The End .....

Pray 4 us a lot ...

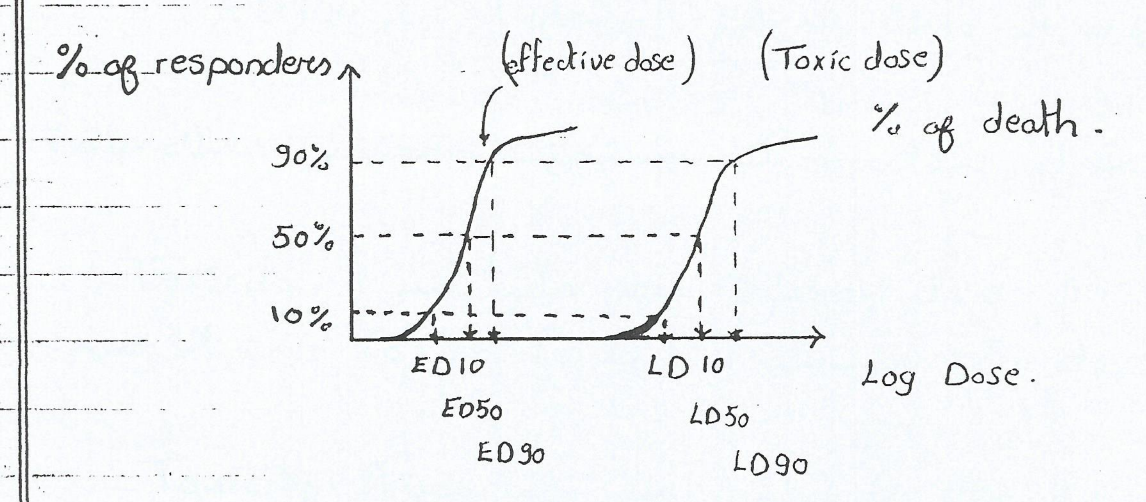


هناك Curve فى الكتاب ولم يشرح فى المحاضرة ولم يقال أصلاً

← هو مهم ← ليه ← علشان يفهمنا ال Therapeutic index

والقانون بتاعه جاء منه اللى هو

$$TI = \frac{LD50}{ED50}$$



⊛ تعالوا نشرح ال curve ده واحدة واحدة علشان نظبطه.

تعالوا نمشى على ال axis بتاع ال Dose وكل شوية نشوف ال effect

وقبل كل حاجة ← ال curve اللى على الشمال هو ال % of responders

يعنى الناس اللى بتتعالج بال dose دى

وال curve اللى على اليمين هو ال % of deaths يعنى الناس اللى بتموت من ال dose دى.

← دلوقتى أنا اديت 100 مريض dose صغيرة أوى ← عشرة منهم فقط إستجابوا لل dose دى والباقى جسمهم لم يتأثر نهائى

ال dose دى هنسميها [ED10]

← إبتديت أزود ال dose ← خمسين منهم إستجابوا والباقى لا.

ال dose دى هنسميها [ED50] ودى مهمة أوى أوى أوى.

→ بدأت أزود ال dose → تسعين استجابوا وعشرة لا
ال Dose دى هنسميها [ED 90]

→ زودت ال dose → كلهم استجابوا → ED 100

→ زودت ال dose → كلك مستجيب ومحدش حصله حاجة

→ زودت ال dose → عشرة منهم ماتوا من ال Toxicity
ال dose دى هنسميها [LD 10] → ودا من ال curve الأيمن

→ زودت ال dose → خمسين منهم ماتوا من ال Toxicity
ال dose دي هنسميها [LD 50] مهمة أوى أوى أوى أوى

→ زودت ال dose → تسعين منهم ماتوا من ال Toxicity
ال dose دى هنسميها [LD 90]

(*) Therapeutic index : $\frac{LD\ 50}{ED\ 50}$

LD 50 ← من ال curve الأيمن
ED 50 ← من ال curve الأيسر

فهمت بقا يا باشا القانون جاي منين ؟
فهمت ال curve كويس ؟

(*) TI **must be** more (1)

, TI → as it ↑ → as the drug Becomes safer.